UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,939	04/12/2004	Tae H. Ji	028750-229	2139

21839 7590 03/22/2007

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,939	JI ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16 and 54-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6 November 2006 has been entered.

Claims 1-15, 17-53 are canceled. Claims 54-56 are new. Claim 16 is amended. Claims 16 and 54-56 are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112, first paragraph – Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 16-17 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement is withdrawn in response to Applicants' cancellation of claim 17 and amendment of claim 16.

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The rejection of claims 16-17 under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement is withdrawn in response to Applicants' cancellation of claim 17 and amendment of claim 16.

Claim Rejections - 35 USC § 102

The rejection of claim 16-17 under 35 U.S.C. 102(b), for being anticipated by Talwar et al. (cited in previous office actions) is withdrawn because of the cancellation of claim 17 and the amendment of claim 16. Specifically, Talwar et al. do not teach the peptide fragments recited in claim 16.

New Rejections

Claim Rejections - 35 USC § 112, first paragraph – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the incidence of pregnancy in a female, comprising administering to a female subject an amount of an agent effective at reducing the incidence of conception, wherein the agent consists of a peptide selected from the group consisting of a peptide consisting of the LHR^{exo2} or LHR^{exo3} does not reasonably provide enablement for the claims as broadly recited. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicants' arguments at p. 4-6 of their remarks will be addressed insofar as they pertain to the current rejection, however, many of the arguments are no longer applicable to the current rejection since the scope of the claims has changed, and the rejection has changed to reflect that change in scope. Paragraph [0304] teaches:

> The specific photoaffinity labeling of hCG by ABG-^{125}I-LHR^{exo3} shows the direct interaction, and this result is consistent with the inhibition of hCG binding to LHR by the peptide, albeit with low affinity. This is a novel and important observation and provides a new insight into the mechanism of the signal generation, particularly considering the recent reports that the exodomain modulates the signal generation by interacting with exoloop 2. Therefore, exoloop 3 interacts with the exodomain, in addition to the interaction with hCG, and participate in the signal generation. Nonlabeled exoloop 2 peptide blocked the labeling of both hCGα and hCGβ as did nonlabeled exoloop 3 peptide, suggesting the competitive nature of their interactions with hCG. Not only exoloop 2 but also the LRR 4 peptide, LHR$^{96-115}$ and the hinge region peptide, LHR$^{246-269}$, inhibited the labeling.

> In contrast, ***the exoloop 1 peptide***...were less potent in the inhibition. The results taken together show the specificity of the labeling and perhaps, interaction between hCG and these regions of LHR, which could provide new insights into the mechanistics of the interaction and signal generation.

This paragraph suggests that only LHR^{exo2} or LHR^{exo3}, but not LHR^{exo1} are capable of interacting with the hCG to inhibit hCG interaction with the exoloop 1, exoloop 2 or exoloop 3 domain of the LHR. Since it is well known in the art that hCG is necessary to sustain early pregnancy, it is biologically plausible that a peptide that inhibits hCG interaction with exoloops 1, 2 or 3 of the LHR, thus inhibiting activation of LHR by hCG could reduce the incidence of conception. However, the recitation of 95-97% identity to the amino acid sequences of the LHR^{exo1} LHR^{exo2} and LHR^{exo3} is too broad given the fact that the instant specification, as indicated by Applicants in their remarks at p. 5, last paragraph, does not teach the specific amino acids that can be added to LHR^{exo1} or LHR^{exo2} or LHR^{exo3}. The recitation in the claim amounts to an invitation to the public to conduct further experimentation to find those mutations of LHR^{exo1} or LHR^{exo2} and/or LHR^{exo3} that bind to hCG and inhibits hCG interaction with the exoloop 1, 2 or 3 domains of LHR. As discussed in the previous Office action mailed 29 June 2006, the development of contraceptive methods comprising administration of the recited peptides encompasses drug discovery and development. Drug discovery is a labor intensive and expensive undertaking, in spite of recent developments in high throughput screening, rational drug design and combinatorial chemistry. According to Swartz and Babelnick, (cited in the office action mailed 27 October 2005), research on and development of novel contraceptives has not kept pace with the growing need, and financial, legal and

political pressures is a barrier to development of new contraceptive products in the United States (see p. 31, column 2, 2nd paragraph and p. 315, column 1, 2nd paragraph). These references provide support for the high level of unpredictability in the art of contraceptive development. In order for a contraceptive device to work, it must be able to inhibit conception and/or implantation of the conceptus, thus the standard for enablement is high given the complexity and unpredictability of this art. Although it is biologically plausible that LHR^{exo2} or LHR^{exo3} could inhibit hCG interaction with the LHR, thus lead to declining hCG levels and early pregnancy loss, other than LHR^{exo2} or LHR^{exo3}, Applicants have only disclosed methods for identifying agents that modulate gonadotropin activity, but well known assays in the art for discovering agents are not equivalent to a positive recitation of how to make said agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Furthermore, with respect to generating mutations of proteins, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions

may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the large number of muteins encompassed by the and screen same for the ability to reduce the incidence of pregnancy in a female, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability in the field of contraceptive development and of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite insufficient structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, first paragraph – Written Description

Claims 16 and 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor

present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of LHR^{exo2} or LHR^{exo3}, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising LHR^{exo2} or LHR^{exo3}, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, first paragraph – New Matter

Claims 16 and 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have added limitations that do not have support in the specification as originally filed. Applicants argue at p. 5., last paragraph that disclosure of a natural sequence is sufficient and cite Ex Parte Bandman. Applicants' arguments are more relevant to enablement than written description and new matter situations, and Ex Parte Bandman is not precedential. Applicants do not specifically contemplate the recited fragments in the specification as originally filed, nor do the those fragments flow naturally from the disclosure. Finally, Applicants cannot rely on prior art for written description in a new matter situation unless they have incorporated a specific prior art by reference in the original disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16, 54-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Hsueh et al. (U.S. Patent 5,925,549, published 20 July 1999). The claims encompass a method comprising administering to a female subject an amount of agent effective at reducing the incidence of conception, wherein the agent comprises a peptide selected from...(see a), b), c) d) of claim 16)...or a sequence at least 97% identical to the amino acid sequence of LHR^{exo1}, LHR^{exo2} or LHR^{exo3}, wherein the peptide binds hCG and inhibits hCG interaction with the exoloop 1, exoloop 2 or exoloop 3 domain of the LHR. Treatment of various female animals are contemplated in claim 55.

The '549 patent discloses soluble glycoprotein binding proteins containing the extracellular portion of the glycoprotein hormone that have contraceptive applications. The exoloop domains of the C-terminal are extracellular as evidenced by Ryu et al (J Biol Chem. 1996; 271: 7301-7304, especially p. 7301, right column, 1st full paragraph and Figure 1, p. 7302). Hsueh et al. define their soluble glycoprotein hormone binding proteins at column 7, lines 4-12:

> The term "soluble glycoprotein hormone binding protein" (sGhBP), refers to a polypeptide containing the extracellular portion of a glycoprotein hormone receptor, such as an LH, FSH or TSH receptor, where the polypeptide has ligand binding properties that are within about an order of magnitude of those associated with the

intact receptor. Examples of sGhBP's are LBP (contains the extracellular portion of the LH receptor), FBP (contains the extracellular portion of the FSH receptor), and TBP (contains the extracellular portion of the TSH receptor).

See also column 6, lines 53-58;

The '549 patent describes the contraceptive applications at column 16, lines 37-47:

C. Contraceptive Applications
Purified soluble LH and FSH binding proteins (i.e., soluble receptors that retain ligand-binding activity) may be used in a number of applications, particularly in fertility and contraceptive applications. Since soluble LH, FSH and CG ligand binding domains produced according to the methods of the present invention are capable of binding to their respective agonist hormones, they can be administered therapeutically to an individual to preferentially neutralize the action of individual gonadotropins by decreasing the availability of the selected gonadotropins to bind to receptors present on the surfaces of target cells.

Treatment of humans, which are primates, are contemplated at column 20, lines 35-37.

Note that the claims recite, "wherein the agent comprises...", thus encompasses either the peptide fragments recited in claim 16, a), b), c) or d) or a larger polypeptide containing the recited fragments. Because the '549 patent discloses that extracelluar regions of the LH receptor are contemplated as soluble glycoprotein hormone binding proteins, and the exoloop domains make up part of the extracelluar domain, the claims are anticipated by the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER